REMARKS

The Office Action Summary states that claim 1 is currently pending and that claims 2-38 have been withdrawn from consideration. Moreover, page 2 of the Office Action states that claim 1 is being examined and "all remaining claims are being held withdrawn from further consideration pending the allowability of generic claim 1."

Pursuant to a restriction requirement from the Office, Applicants elected to prosecute the claims of Group I where X is sulfur. With this response, Applicants have amended the claims such that X is only sulfur and have canceled all claims where X is not sulfur. Claims 1-4, 11-13, 17-18, 20-24, 26-27, 29-30 and 33-38, accordingly, are presently pending. Consistent with MPEP chapter 800, Applicants respectfully request for the Office to examine all pending claims of the elected group, claims 1-4, 11-13, 17-18, 20-24, 26-27, 29-30 and 33-38.

I. 35 U.S.C. 103 Rejection in view of Rimbault et al.

A. Claim 1 is not obvious in view of the disclosure of Rimbault et al.

Reconsideration is requested of the rejection of claim 1 under 35 U.S.C.103 in view of Rimbault et al.

Claim 1 is directed toward a genus of compounds of Formula I". The structures of claim 1, which are COX-2 selective inhibitors, are benzopyrans.

Rimbault et al. disclose a genus of flavene and thioflavene derivatives. The compounds are said to be active in stimulating the mucociliary transport in bronchia. Because of this stimulatory activity, Rimbault et al. disclose that the compounds may be used to treat diseases of the respiratory tract such as chronic bronchitis.

According to the Office, "Rimbault et al teach a genus of compounds which when Y is S and one of X1 and X2 is free or functionalized carboxy and the other is halogen, etherified OH, or nitro are positional isomers of the instant compounds when X is S, A1-A4 is C, R" is phenyl, R is carboxyl or functionalized

carboxyl and R1 is chloro, nitro or alkoxy."[1] The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient to establish a prima facie case of obviousness.[2] There still must exist some motivation or suggestion to make the claimed invention. When considering the motivation, the Office should take into consideration the size of the genus. In this case, the Office has not shown sufficient motivation to make the needed selection.

In *re Baird et al.*[3] the issue of what constitutes sufficient motivation to make such a selection was considered. In *in re Baird*, the claimed invention was directed towards a flash fusible toner comprising a polyester of bisphenol A and an aliphatic dicarboxylic acid. The Examiner rejected the inventors'claims as obvious stating that the prior art [i.e., Knapp] "clearly encompassed the generic disclosure of the claimed invention and provided ample motivation to make the necessary selection." [4] The Board upheld the Examiner's rejection. The Court, however, reversed the rejection stating that

> ...the generic diphenol formula disclosed in Knapp contains a large number of variables, and we estimate that it encompasses more than 100 million different diphenols, only one of which is bisphenol A [i.e., the compound of the claimed invention.] While the Knapp formula unquestionably encompasses bisphenol A when selected variables are chosen, there is nothing in the disclosure of Knapp suggesting that one should select such variables.[5]

Analogous to the prior art cited in *in re Baird*, there is no motivation in Rimbault et al. to make a compound of claim 1. Rimbault et al. disclose a genus of flavene and thioflavene derivatives having formula I that includes three different variables where the number of different possible combinations of variables totals several thousand to potentially a million different compounds. The Office contends that claim 1 is obvious because if a skilled artisan were to select specific substitutes for Y, X1 and X2, then the prior art compound would

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[1] See Paper 12123 at page 2.
[2] *In re Baird*, 16 F.3d 380, 29 U.S.P.Q 1150, 1552 (Fed. Cir. 1994).
[3] *In re Baird, et al.*, 29 USPQ2d 1550.
[4] *Id.* at 1551
[5] *Id*

be a positional isomer of a compound recited in claim 1. Nowhere, however, as *in re Baird*, does the disclosure of Rimbault et al. suggest that one should select the Office's exact recitation of variables from the potentially million possible combinations. Without this prerequisite motivation to make such a selection, the Office has not established a *prima case* of obviousness.

The Office has stated that "positional isomers in the chemical art are considered to be obvious variants, wherein an ordinary skilled artisan would be motivated to prepare one of a known compound with a reasonable expectation that it would possess the same or similar properties as its known counterpart, absent some unobvious or unexpected results". This is not correct.

The properties of different isomers of the same compound can be markedly different from each other. In fact, sometimes, the differences in chemical and physical properties are so great, that the isomers are assigned to different chemical families. This is the case for example with ethyl *alchohol* and dimethyl *ether* (Morrison and Boyd, Organic Chemistry, 6th Edition, 1992, Prentice Hall, p 36). Ethyl alcohol is a compound with a liquid boiling point of 78°C, yet, dimethyl ether is a gas with a boiling point of -24°C. Both compounds contain carbon, hydrogen, and oxygen in identical proportions of 2C:6H:1O. The two compounds differ not only in their physical properties, but also in their chemical properties. For instance, ethyl alcohol is a very reactive compound. If a piece of sodium metal is dropped into a test tube containing ethyl alcohol, there is vigorous bubbling and the sodium metal is consumed, hydrogen gas is evolved, and a compound of formula C_2H_5ONa is left. Ethyl alcohol also reacts with hydriodic acid to form water and a compound of formula C_2H_5I. In contrast, dimethyl ether does not react at all with sodium metal. In addition, although like ethyl alcohol, it reacts with hydriodic acid, it yields a compound of formula CH_3I instead of C_2H_5I. The two compounds have the same molecular weight of 46 and the same molecular formula of C_2H_6O.

Moreover, structural isomerism can also influence a compound's affinity for a specific receptor site and its intrinsic pharmacologic activity. For example, seizure activity was first associated with patients treated with methohexital.

However, subsequent fractionation of the original compound into its two isomeric forms resulted in the identification of the isomer primarily responsible for the convulsive activity. The inhaled anesthetic flurothyl (hexaflurodiethyl) ether and the intravenous anesthetic ketamine also illustrate how subtle changes in stereoisomerism can result in significant changes in structure-activity relationships. Flurothyl, a fluorinated ether analogue, reliably produces convulsions in nonepileptic patients, whereas its structural isomer isoindoklon has not been associated with seizure activity.

In the present case, in fact, several sets of positional isomers having formula 1 were tested for COX-1 and COX-2 inhibitory activity. The assay performed and compounds tested are detailed in the Declaration of Dr. Jeffery Carter, a copy of which is enclosed with this response. As stated by Dr. Carter, in his declaration, each of the positional isomers has "markedly different activity." (Paragraph 3 of Jeffery Carter Declaration).

Accordingly, contrary to the Office's contention, a skilled artisan would not be motivated to prepare a compound of claim 1 based upon the disclosure of Rimbault et al., because a skilled artisan would recognize that positional isomers often have very different pharmokinetic activity even when they are structurally very similar. This principle is illustrated by the Declaration of Dr. Carter, which states that positional isomers having formula I have markedly different COX-1 and COX-2 inhibitory activity.

In view of the foregoing, Applicants respectfully request that the rejection of claim 1 be withdrawn. Claims 2-4, 11-13, 17-18, 20-24, 26-27, 29-30, and 33-38 incorporate all of the claim 1 requirements and are therefore, patentable over Rimbault et al. for all of the reason stated for claim 1 and by reason of the additional requirements that they introduce.

Moreover, in each of claims 3, 4, 12, 13, 18, 20-24, 26, 29, and 30 R" cannot be phenyl. When R" is not phenyl, the compound of the current invention, as acknowledged by the Office, is not a positional isomer of the compound disclosed in Rimbault et al. Accordingly, claims 3, 4, 12, 13, 18, 20-24, 26, and

29-30 are not obvious in view of Rimbault et al. because Rimbault et al. does not even disclose the claimed compounds.

In addition, claim 33 is directed toward a method of treating a COX-2 mediated disorder in a subject by administering to the subject a compound of Claim 1. Rimbault et al. disclose that the disclosed compounds have efficacy in "stimulating the mucociliary transport in bronchia." Nowhere do Rimbault et al. disclose or suggest that the disclosed compounds are COX-2 inhibitors. In view of this, claim 33 is not obvious in view of Rimbault et al. Claims 34-38 incorporate all of the claim 33 elements and are therefore, patentable over Rimbault et al. for all of the reasons stated with respect to claim 33 and by reason of the additional requirements they introduce.

B. Claim 1 is not obvious in view of the disclosure of Funicello et al.

Reconsideration is requested of the rejection of claim 1 under 35 U.S.C. 103 (a) in view of Funicello et al.

Claim 1 is directed toward a genus of compounds of Formula I". The structures of claim 1, which are COX-2 selective inhibitors, are benzothiophenes.

Funicello et al. generally disclose the thermal reactivity of 2-azido- and 3-azido-benzo[b]thiophene with alkenes. The cited art discloses a number of compounds that are intermediates in this reaction. Nowhere, however, does the reference disclose or suggest a utility for any of the disclosed compounds.

According to the Office, "Funicello et al teach compounds of the formula II which when R is CO2Me are positional isomers of the instant compounds when X is S, A1-A4 is C, R" is H, R, is alkoxycarbonyl and R1 is cyano."[6] The fact that a claimed species or subgenus is encompassed by the prior art is not sufficient by itself to establish a *prima facie* case of obviousness. There still must be some suggestion or motivation to make the claimed invention. For all of the reasons detailed above in IA, and analogous to the facts detailed in *In re Baird*, the Office has not established that Funicello et al. provides a skilled artisan with the necessary teaching or suggestion to make a compound of claim 1.

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[6] Funicello *et al.*

Moreover, as detailed in MPEP 2144.08, close structural similarity alone is not sufficient to create a *prima facie* case of obviousness when the reference does not disclose a utility for the compounds because "there is no motivation to make related compounds."[7] Also a lack of any known useful properties weighs against a finding of motivation to make or select a species or subgenus.[8] Nowhere do Funicello et al. disclose a utility for any of the disclosed compounds. The compound that the Office has cited against claim 1 (i.e., the triazoline on page 2974 in figure 12) is simply an intermediate in the cycloaddition reaction disclosed in the article. Because no utility is disclosed, the Office has not established that Funicello et al. provides a skilled artisan with the necessary teaching or suggestion to make a compound of claim 1.

In addition, claim 33 is directed toward a method of treating a COX-2 mediated disorder in a subject by administering to the subject a compound of Claim 1. Nowhere do Funicello et al. disclose or suggest that the disclosed compounds are COX-2 inhibitors. In view of this, claim 33 is not obvious in view of Funicello et al. Claims 34-38 incorporate all of the claim 33 elements and are therefore, patentable over Funicello et al. for all of the reasons stated with respect to claim 33 and by reason of the additional requirements they introduce.

In view of the foregoing, Applicants respectfully request that the rejection of claim 1 be withdrawn. Claims 2-4, 11-13, 17-18, 20-24, 26-27, 29-30, and 33-38 incorporate all of the claim 1 requirements and are therefore, patentable over Funicello et al. for all of the reason stated for claim 1 and by reason of the additional requirements that they introduce.

II. Conclusion

In light of the foregoing Applicants request entry of the claimed amendments, withdrawal of the claim rejections and solicit and allowance of the

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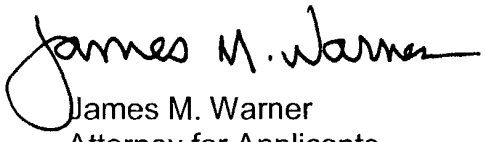
[7] See, e.g., In re Albrecht, 514 F.2d 1389, 185 U.S.P.Q. 585 (CCPA 1975).
[8] *Id.*

claims. The Examiner is invited to contact the undersigned Attorney should any issues remain unresolved,

Respectfully submitted,



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